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RESEARCH ARTICLE

LETROZOLE VERSUS CLOMIPHENE AS FIRST LINE OF TREATMENT IN SUB-FERTILE COUPLES - A PROSPECTIVE RANDOMIZED TRIAL

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ABSTRACT

Background: Super ovulation and Intrauterine insemination is an effective treatment for infertile couples. Probability of pregnancy is increased by increasing the number of oocytes available and by correcting any subtle defects of ovulation. Clomiphene citrate has been the first line of treatment for subfertile couples for quite some time. Letrozole also has been successfully used for the ovulation induction and in contrast to Clomiphene Citrate, it does not deplete the estrogen receptors. Objective of this study is to compare Letrozole 2.5 mg and Clomiphene Citrate 100 mg as first line ovulation induction drug in sub-fertile women. **Methods:** 126 Treatment naive sub-fertile women were randomized to treatment with 2.5 mg Letrozole (63 Patients) or 100 mg Clomiphene Citrate (63 Patients) daily starting day 2 to 6 of menstrual cycle. Intra Uterine Insemination (IUI) was carried out 36 to 40 hrs after Human Chorionic Gonadotrophin (HCG) injection. Ovulation rate, endometrial thickness, pregnancy rate were compared and analyzed. Results: The groups were randomized so that the mean Body Mass Index (BMI), age and duration of infertility in both the groups were similar. Ovulation rate was 66.67% (42/63) in Letrozole group and 74.60% (47/63) in Clomiphene group. The median endometrial thickness on the day of hCG showed no significant difference between Letrozole group and clomiphene group. It was 8.1mm. Pregnancy rate in the Letrozole group was 9.52% (6/63) and in the Clomiphene group was 7.94% (5/63). Conclusion: No significant difference was seen between clomiphene citrate and letrozole as both have a comparable clinical pregnancy rate. However, letrozole has the advantage of development of fewer follicles; hence it may reduce the risk of multiple pregnancies.

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INTRODUCTION

A common cause of sub-fertility in couples is anovulation (Homburg, 2005). Superovulation and Intrauterine insemination is an effective treatment for infertile couples (Costello, 2004). Probability of pregnancy is increased by increasing the number of oocytes available and by correcting any subtle defects of ovulation. Increase in the concentration of active motile sperms and their placement in the uterine cavity with IUI, overcomes the male factors and cervical factors of infertility (Guzick, 1998). Clomiphene citrate has been the first line of treatment for subfertile couples but its anti-estrogenic effects on the endometrium and the endocervix have proven to be its major drawbacks (Massai, 1993; Nelson, 1990).

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Letrozole was introduced, much later and is usually regarded as the second line of treatment. The dose of Letrozole 2.5 mg, an aromatase inhibitor, gives a monofollicular response, does not adversely affect the cervical mucous or the endometrium unlike clomiphene (Mitwally, 2001; Azim, 2007). In the last few years, Letrozole has been successfully used for the ovulation induction (Pritts, 2010; Requena et al., 2008) and in contrast to Clomiphene Citrate, it does not deplete the estrogen receptors (Cortinez, 2005; Holzer, 2006). Optimal dose and duration of Letrozole is still not clear. It has been administered for variable periods, from day 1 to day 10 of Menstrual cycle, daily from 2.5 to 7.5 mg/day (Pritts, 2010). Al-Fadhli et al found a higher pregnancy rate with 5 mg/day compared with 2.5 mg a day (Al-Fadhli, 2006). Badawy et al reported a higher pregnancy rate with an extended Letrozole regimen of 2.5 mg/day from day 1 to day 10 of menstrual cycle (Badawy, 2009). The aim of this randomized controlled trial was to compare the efficacy of

Letrozole vs Clomiphene Citrate in the treatment of sub-fertile couples.

METHODS

126 patients were randomized into two equal groups. The first group received Letrozole 2.5 mg a day. The second group received Clomiphene Citrate 100 mg a day. Both were given from day 2 to day 6 of menstrual cycle. Transvaginal Ultrasonography was done, from day 10 onwards. The hCG (Human Chorinic Gonadotropin) (10000 IU) was administered for ovulation when at least one mature follicle was $\geq$ 18 millimetres. Intra-uterine insemination was done at 36 to 40 hrs after hCG trigger. Urine pregnancy test was performed 17 days after IUI.

RESULTS

A total of 126 patients were recruited in the study with each group having 63 patients. There were no significant differences between both groups with respect to age, body mass index, duration of infertility, percentage of patients with primary or secondary infertility (Table 1). There was statistically significant difference with regard to total number of follicles, follicles more than 18 mm on the day of hCG administration, serum E2 levels and the endometrial thickness in both groups (Table 2). However, the difference in the pregnancy rates between the two groups, which is the target of treatment, was not significant (Table 2).

DISCUSSION

The results of our study revealed that Letrozole is similar to clomiphene citrate as a first line treatment of sub-fertile women. Efficacy of Clomiphene citrate was found to be variable among all situations of ovulation. About 15% to 19% of the patients were resistant to clomiphene citrate in our study. Poor cervical mucous and thinning of endometrium was also associated with 15% to 45% pf our patients who were on prolonged clomiphene citrate treatment. This may be caused by prolonged estrogen receptor depletion in endometrium and may be in cervix also (Gonen, 1990; Yagel, 1992). Aromatase inhibitors such as Letrozole has been used as an alternative to clomiphene citrate to avoid this problem, but it is unclear if these aromatase inhibitors are as effective in ovulation induction as clomiphene citrate. A third generation aromatase inhibitor, letrozole, which is a type IIa aromatase inhibitor, was thought to increase follicle stimulating hormone secretion by blocking estrogen. The short half life of letrozole is advantageous as its effect decreases during late follicular phase and therefore Estradiol produced by growing follicles increases. The elevated Estradiol levels suppress the release of FSH. The drop in FSH levels causes atresia of all follicles smaller than the dominant follicle leading to mono-ovulation in most cycles.

Use of letrozole 2.5 mg was described for ovulation induction by Mitwally and casper (Mitwally, 2001), who reported 75% success in ovulation and pregnancy in 25% of their patients. In contrast clomiphene citrate induces prolonged estrogen receptors depletion in the brain and therefore the increased Estradiol produced by the growing follicles is not capable of suppression of FSH release. This maintains the release of high levels of FSH throughout the follicular phase and therefore induces development of multiple follicles. The main advantage of induction of ovulation with letrozole in patients with PCOS who are often hyper responders and at high-risk for OHSS, multiple ovulation is desired in patients with unexplained infertility undergoing IUI. Even though letrozole induced fewer mature follicles as compared to clomiphene citrate the pregnancy rate is still comparable between both management options (Requena, 2008; Polyzos, 2008) because it has no adverse effects on the endometrium. Considering the much higher per cycle cost of letrozole compared to clomiphene citrate and almost equal pregnancy rates, we did not find any significant advantage of using letrozole over clomiphene citrate.

Table 1. Characteristics of Patients

Characteristic	Letrozole group(n=63)	Clomiphene citrate group(n=63)	P value
No of cycles	195	192	
Age(years)	27.1 + 3.3	28.9 + 2.8	.52
Body mass index (kg/m 2	26.25 + 3.52	25.34 + 4.04	.112
Duration of infertility (yrs)	3.67 + 1.86	3.40 + 1.68	.226
Primary infertility	41/63 (65.08%)	43/63 (68.25%)	.301
Secondary infertility	22/63 (34.92%)	20/63 (31.75%)	.121

Note: None of P values were statistically significant (P> .05)

Table 2. Outcome in letrozole and clomiphene citrate groups

Outcome	Letrozole group(n=63)	Clomiphene citrate group(n=63)	P value
Number of cycles	195	192	
Total no of follicles	4.3 $\pm$ 0.4	6.7 $\pm$ 0.3	.04[a]
Number of follicles more than 18 mm	2.2 $\pm$ 0.1	3.0 $\pm$ 0.7	.03[a]
Endometrial thickness at hCG (mm)	8.2 $\pm$ 0.2	9.3 $\pm$ 0.6	.02[a]
Serum E2 (pg/ml)	256.2 $\pm$ 65.1	386.2 $\pm$ 89.9	.02[a]
Pregnancy/ cycle	29/195 (14.87)	32/192 (16.67)	.70

[a]Statistically significant: P< 0.05

Conclusion

There is no significant advantage of using letrozole over clomiphene citrate in sub-fertile women. However, letrozole may have advantage of having a comparable clinical pregnancy rate with the advantage of development of fewer follicles, hence it may reduce the risk of multiple pregnancies. Further studies with larger sample size are required to authenticate the findings.

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